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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,786	08/27/2003	Jian Ni	1488.130000B/EKS/EJH	5264
28393 7590 01/09/2007 STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C. 1100 NEW YORK AVE., N.W. WASHINGTON, DC 20005			EXAMINER KAUFMAN, CLAIRE M	
			ART UNIT	PAPER NUMBER
			1646	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		01/09/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/648,786	<b>Applicant(s)</b> NI ET AL.	
	<b>Examiner</b> Claire M. Kaufman	<b>Art Unit</b> 1646	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 30 October 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-77 is/are pending in the application.
- 4a) Of the above claim(s) 1-25,31,32,45-48,50,69-72 and 74 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 26-30,33-44,49,51-68,73 and 75-77 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-77 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>4/12/04,4/12/04,9/30/04,9/8/05</u> | 6) <input type="checkbox"/> Other: _____  |

**DETAILED ACTION*****Election/Restrictions***

Applicant's election with traverse of 1) an anti-DR4 antibody which is an agonist, 2) a disease which is cancer, 3) a second therapeutic which is a chemotherapeutic, and 4) a chemotherapeutic which is a platinum analog, in the reply filed on 10/26/06 is acknowledged. The traversal is on the ground(s) that the search for treatment of one disease with a DR4 antibody would lead to finding publications that disclose using DR4 antibodies for treating other diseases; the search for a therapeutic agent to treat a disease would lead to publications disclosing other therapeutic agents; and the search for a platinum analog for treatment would lead to publications disclosing other chemotherapeutics for treatment. This is not found persuasive because the search for one disease will not necessary lead to disclosure of other diseases that can be treated the same way because publications which are not reviews generally do not focus on a variety of diseases but are written to investigate a single disease or limited number of highly related diseases, of which it is maintained the species of claimed diseases are not, and even reviews tend to have limited scopes. This reasoning is also why the search for one therapeutic or chemotherapeutic would not necessarily lead to a publication disclosing others, namely that each disease requires therapeutics with particular properties and different cancers and patient populations require different chemotherapeutics. Contrary to applicants' assertion that any search of the prior art in regard to one species will reveal whether any prior art exists as to the other species, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. It is noted that applicants do not say that treatment of one disease would have been obvious over treatment of another disease using a DR4 antibody. Nor that use of one therapeutic would have been obvious over another. As stated in the previous Office action in the paragraph bridging pages 4-5:

The diseases listed are distinct and literature for one would not necessarily discuss the others. The second therapeutic agents are structurally and functionally distinct, for example, even chemotherapeutic agents have different targets and effects. Also, searches for an invention require identification of prior art that makes obvious in addition to that which anticipates the claims. Therefore, the searches for different species are not the same.

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Applicants included *In re Weber* and *In re Haas* with their response, though neither case was discussed by Applicants. These cases deal with improper Markush claims. The claims in the instant application are not improper Markush claims and so are subject to a species election.

The requirement is still deemed proper and is therefore made FINAL.

Claims 26-30, 33-44, 49, 51-68, 73 and 75-77 encompass the elected species and are here examined.

### ***Title***

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested:

Death Domain Containing Receptor-4 Antibodies And Methods

### ***Specification***

Applicants are required to use the heading "Brief Description of the Drawings" instead of "Brief Description of the Figures" at page 10. See MPEP 608.01(f)

### ***Drawings***

When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and a sequence identifier ("SEQ ID NO:X") must be used either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02. In the instant application, a sequence identifier must be used for the amino acid and nucleotide sequence of DR4 appearing in the Figures, see for example Figs. 1 and 2.

Appropriate correction is required.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

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improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-30, 33-36, 40, 42- 44, 51-62, 66, 68 and 75-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 14, 26, 28, 40, 42, 54, 56, 66, 68, 78, 80, 90, 92, 102, 104, 116, 118, 130, 132, 144, 146, 158, 160, 170, 172, 182, 184, 194, 196, 209, 211, 212, 214, 215, 217, 218 and 220 of U.S. Patent No. 7,060,272.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims are drawn to either a method of inducing apoptosis or treating cancer by administering both an antibody that binds DR4 or the extracellular domain thereof and a chemotherapeutic agent, or to a composition comprising the antibody and a chemotherapeutic agent. Note that patent claim 139, for example, designate the antibody as being a chimeric, Fab fragment or F(ab') fragment, and claims 137 and 138 designate the antibody as being monoclonal or polyclonal. Claim 9, for example, designates that antibody is labeled with an enzyme, which is a heterologous polypeptide.

Claims 37-41 and 63-67 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 14, 26, 28, 40, 42, 54, 56, 66, 68, 78, 80, 90, 92, 102, 104, 116, 118, 130, 132, 144, 146, 158, 160, 170, 172, 182, 184, 194, 196, 209, 211,

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212, 214, 215, 217, 218 and 220 of U.S. Patent No. 7,060,272 as applied above and in view of U.S. 6,025,158.

US 7,060,272 does not claim single chain, humanized, human or pegylated antibodies.

U.S. 6,025,158 teaches antibodies for treatment which are single chain (*e.g.*, col. 12, lines 26-40), humanized (*e.g.*, col. 59, lines 50-67), human (*e.g.*, col. 38, lines 55-64) and pegylated (*e.g.*, col. 43, lines 21-62), which were well known in the art at the time the invention was made.

Because these types of antibodies were well known at the time the invention was made and their advantages were recognized as shown in US 6,025,158, having the methods and compositions of US 7,060,272 comprise antibodies with these characteristics would have been obvious at the time the invention was made.

Claims 49 and 73 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 14, 26, 28, 40, 42, 54, 56, 66, 68, 78, 80, 90, 92, 102, 104, 116, 118, 130, 132, 144, 146, 158, 160, 170, 172, 182, 184, 194, 196, 209, 211, 212, 214, 215, 217, 218 and 220 of U.S. Patent No. 7,060,272 as applied above and in view of Base et al. (Int. Urology and Nephrology 16(2):157-164, 1984).

US 7,060,272 does not claim a platinum analogue as a chemotherapeutic.

Base et al. teach the advantage of using cis-platin as a chemotherapeutic for the treatment of certain testicular tumors, reporting that "The adoption of cis-platin in the treatment of malignant testicular tumours by Einhorn and Donohue meant a major contribution."

It would have been obvious at the time the invention was made to use a platinum analog such as cis-platinum as a chemotherapeutic because such analogues were old in the art and recognized as having important chemotherapeutic properties as exemplified in Base et al.

Claims 26-30, 33-44, 49, 51-68, 73, 75-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-146 of U.S. Patent No. 6,461,823 in view of Base et al. (Int. Urology and Nephrology 16(2):157-164, 1984), U.S. Patent Nos. 6,025,158 and 5,763,223.

U.S. Patent No. 6,461,823 claims antibodies which bind DR4 [SEQ ID NO: 2 (or encoded by the cDNA contained in ATCC# 97853)] or a portion thereof, including the extracellular domain. Note that patent claim 4, for example, designates the antibody as being a chimeric, Fab fragment or F(ab') fragment, and claims 59 and 60 designate the antibody as being monoclonal or polyclonal. Claim 6, for example, designates that the antibody is labeled with an enzyme, which is a heterologous polypeptide. US 6,461,823, does not claim treatment of cancer, pegylation of the antibody, a human or humanized antibody or combining the antibody with a platinum analog.

US 5,763, 223 teaches using TRAIL to induce apoptosis in cancer cells for treating cancer (*e.g.*, col. 1, lines 60-63).

U.S. 6,025,158 teaches antibodies for treatment which are single chain (*e.g.*, col. 12, lines 26-40), humanized (*e.g.*, col. 59, lines 50-67), human (*e.g.*, col. 38, lines 55-64) and pegylated (*e.g.*, col. 43, lines 21-62), which were well known in the art at the time the invention was made.

Base et al. teach the advantage of using cis-platin as a chemotherapeutic for the treatment of certain testicular tumors, reporting that "The adoption of cis-platin in the treatment of malignant testicular tumours by Einhorn and Donohue meant a major contribution."

It would have been obvious at the time the invention was made to use an anti-DR4 antibody to treat cancer because DR4 bound TRAIL, which binding induced apoptosis (see Fig. 6A and col. 6, lines 44-48, of US 6,461,823) and TRAIL was disclosed by US 5,763,223 as having the ability to induce apoptosis in cancers. Therefore, an antibody that bound and activated DR4 would have reasonably been expected to have TRAIL-like apoptosis inducing activity. It further would have been obvious to use a platinum analog such as cis-platinum as a chemotherapeutic with an anti-DR4 antibody because such analogues were old in the art and recognized as having important chemotherapeutic properties as exemplified in Base et al. Further, because single chain, human, humanized and pegylated of antibodies were well known at the time the invention was made and their advantages were recognized as shown in US 6,025,158, having the methods and compositions of US 6,461,823 comprise antibodies with these characteristics would have been obvious at the time the invention was made.

Claims 26-30, 33-44, 49, 51-68, 73, 75-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-146 of U.S. Patent No. 6,943,020 in view of Base et al. (Int. Urology and Nephrology 16(2):157-164, 1984), U.S. Patent Nos. 6,025,158 and 5,763,223.

U.S. Patent No. 6,943,020 claims antibodies which bind DR4 [SEQ ID NO: 2 (or encoded by the cDNA contained in ATCC# 97853)] or a portion thereof, including the extracellular domain. Note that patent claim 5, for example, designates the antibody as being a chimeric, Fab fragment or F(ab') fragment, and claims 4 and 3 designate the antibody as being monoclonal or polyclonal. Claim 7, for example, designates that the antibody is labeled with an enzyme, which is a heterologous polypeptide. US 6,943,020, does not claim treatment of cancer, pegylation of the antibody, a human or humanized antibody or combining the antibody with a platinum analog.

US 5,763, 223 teaches using TRAIL to induce apoptosis in cancer cells for treating cancer (col. 1, lines 60-63).

U.S. 6,025,158 teaches antibodies for treatment which are single chain (*e.g.*, col. 12, lines 26-40), humanized (*e.g.*, col. 59, lines 50-67), human (*e.g.*, col. 38, lines 55-64) and pegylated (*e.g.*, col. 43, lines 21-62), which were well known in the art at the time the invention was made.

Base et al. teach the advantage of using cis-platin as a chemotherapeutic for the treatment of certain testicular tumors, reporting that "The adoption of cis-platin in the treatment of malignant testicular tumours by Einhorn and Donohue meant a major contribution."

It would have been obvious at the time the invention was made to use an anti-DR4 antibody to treat cancer because DR4 bound TRAIL, which binding induced apoptosis (see Fig. 6A and col. 6, lines 44-48, of US 6,943,020) and TRAIL was disclosed by US 5,763,223 as having the ability to induce apoptosis in cancers. Therefore, an antibody that bound and activated DR4 would have reasonably been expected to have TRAIL-like apoptosis inducing activity. It further would have been obvious to use a platinum analog such as cis-platinum as a chemotherapeutic with an anti-DR4 antibody because such analogues were old in the art and recognized as having important chemotherapeutic properties as exemplified in Base et al. Further, because single chain, human, humanized and pegylated antibodies were well known at the time the invention was made and their advantages were recognized as shown in US

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6,025,158, having the methods and compositions of US 6,943,020 comprise antibodies with these characteristics would have been obvious at the time the invention was made.

***Claim Rejections - 35 USC § 112, Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is indefinite because it recites administering “therapeutically effective amounts” of a first and second agent. Because the word “amounts” is plural, it is unclear if the administration must occur more than once. If the claims do not require multiple administrations, changing “amounts” to the singular form would obviate this rejection.

***Claim Rejections - 35 USC § 112, First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28, 30, 33-44, 49, 51, 52, 54, 56, 58-68, 73, 75 and 77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. When biological material is required to practice an invention, and if it is not so obtainable or available, the enablement requirements of 35 USC §112, first paragraph, may be satisfied by a deposit of the material. See 37 CFR 1.802.

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The specification does not provide a repeatable method for obtaining ATCC Deposit No. 97853, and it does not appear to be a readily available material. For each deposit made pursuant to these regulations, the specification shall contain: (1) The accession number for the deposit; (2) The date of the deposit; (3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and (4) The name and address of the depository. [See MPEP 2404-2410.02.]

The location and date of deposit of ATCC #97853 is disclosed in [0035]; however, the deposit does not satisfy the enablement requirements. If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or Declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification. In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

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***Priority***

It is noted that the earliest provisional application 60/035,722, filed 1/28/97, to which the instant application claims benefit of priority discloses both the structure and sequence of the protein (SEQ ID NO:2) to which the antibody of the claims binds, as well as the activity of the receptor--the ability to induce apoptosis, and agonist antibodies.

***Alternative Names***

DR4 is also known as TRAIL-1, APO4, TNFRSF10A, TRAIL-R1, TR4 and TR6.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

January 4, 2007